

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
28 July 2005 (28.07.2005)

PCT

(10) International Publication Number
WO 2005/067887 A2

(51) International Patent Classification⁷: **A61K 9/00**

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:
PCT/IS2005/000008

(22) International Filing Date: 23 March 2005 (23.03.2005)

(25) Filing Language: English

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: English

(30) Priority Data:

7196 24 March 2004 (24.03.2004) IS
7772 23 March 2005 (23.03.2005) IS

(71) Applicant (for all designated States except US): ACTAVIS GROUP [IS/IS]; Reykjavikurvegur 76-78, IS-222 Hafnarfjordur (IS).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

(72) Inventor; and

Published:

(75) Inventor/Applicant (for US only): REYNIR, Eyjolfsson [IS/IS]; Eyrarholt 6, IS-220 Hafnarfjordur (IS).

- upon request of the applicant, before the expiration of the time limit referred to in Article 21(2)(a)
- without international search report and to be republished upon receipt of that report
- without classification; title and abstract not checked by the International Searching Authority

(74) Agent: A & P ARNASON; Efstaleiti 5, 103 Reykjavik (IS).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/067887 A2

(54) Title: FORMULATIONS OF RAMIPRIL

(57) Abstract: The present invention relates to stable tablet formulations of ramipril, optionally in combination with a diuretic.

Formulations of Ramipril

FIELD OF THE INVENTION

5

The present invention relates to stable pharmaceutical formulations of ramipril, optionally in combination with a diuretic.

TECHNICAL BACKGROUND AND PRIOR ART

- 10 Ramipril, (2S,3aS,6aS)-1[(S)-N-(S)-1-carboxy-3-phenylpropyl] alanyl octahydrocyclopenta[b]pyrrole-2-carboxylic acid, 1-ethyl ester is an angiotensin converting enzyme (ACE) inhibitor. Ramipril is used for the treatment of hypertension, heart failure, stroke, myocardial infarction, diabetes and cardiovascular disease.
- 15 Ramipril and the acid form, ramiprilat, is described in EP 0 097 022 B1.

The preparation of stable pharmaceutical formulations of ramipril is complicated since it is susceptible to certain types of degradation. Ramipril can undergo cyclization via internal nucleophilic attack to form substituted diketopiperazines and also degrade via hydrolysis and oxidation.

EP 1 501 546 A1 describes stable pharmaceutical formulation for combinations of a statin and an ACE inhibitor. The problem underlying the invention is that if an ACE inhibitor is in the presence of a stabilised statin, the
25 ACE inhibitor decomposes to such extent that even after short storage period the content of decomposition products exceeds the permissible limit of degradation. EP 1 501 546 A1 provides a formulation wherein the statin and the ACE inhibitor are separated by physiologically acceptable inert material. Calcium sulfate is mentioned as a possible inorganic filler in the formulation
30 but it is neither claimed nor mentioned in any example. In fact all the examples are concerned with three-layer tablet, wherein the statin layer and

ACE inhibitor layer are separated by a layer of microcrystalline cellulose. Combinations of the ACE inhibitor with a diuretic are not mentioned.

US 2003/0215526 claims formulations of ACE inhibitor a pharmaceutical composition comprising a therapeutically effective amount of an ACE inhibitor which is susceptible to degradation or its salt; a greater than stoichiometric amount of an alkali or alkaline earth metal carbonate, relative to the amount of ACE inhibitor or its salt, and a pharmaceutically acceptable carrier. The excipient calcium sulphate is not mentioned.

EP 0 280 999 B1 describes a composition comprising ACE inhibitor (i.e. ramipril), an alkali or alkaline earth metal carbonate and saccharide wherein the ACE inhibitor is stabilized against degradation (cyclization, discoloration and hydrolysis) by means of the other mentioned ingredients. In the specifications the relevant saccharides are lactose and mannitol. Modified starch is mentioned as disintegrant in the specification.

EP 0 317 878 B1 claims a stable, compressed pharmaceutical formulation containing a compound of a defined formula (i.e. ramipril) wherein, for stabilization before compression, a compound of the formula is a) coated with a polymeric, physiologically tolerated protective coating, or b) mixed with a physiologically tolerated buffer which ensures that a pH in the weakly acidic to weakly alkaline range is set up in a pharmaceutical formulation in the presence of moisture, where sodium bicarbonate is excepted as buffer, or c) mixed with a physiologically tolerated buffer which ensures that a pH in the weakly acid to weakly alkaline range is set up in a pharmaceutical formulation in the presence of moisture, and is coated with a polymeric, physiologically tolerated protective coating, where, in the case of stabilization according to b) with alkali metal or alkaline earth metal carbonate, the formulation is free of sugar.

WO 93/17685 claims combinations of ACE inhibitors and diuretics such as hydrochlorothiazide. Sodium hydrogen carbonate, pregelatinised starch and magnesium stearate are mentioned as excipients. Calcium sulphate is not mentioned.

Compositons of ramipril and piretanide is described in EP 215 357 B1. Calcium sulfate is not mentioned in this patent.

WO 03/028707 claims a formulation containing ramipril and lactose monohydrate. Calcium sulfate is mentioned in the specification as a possible diluent. Calcium sulfate is not included in any example.

SUMMARY OF THE INVENTION

10

In an attempt to prepare a stable tablet formulation of ramipril, it was discovered that useful formulations can be produced by the use of calcium sulphate dihydrate (e.g. Compactrol) as filler material.

15

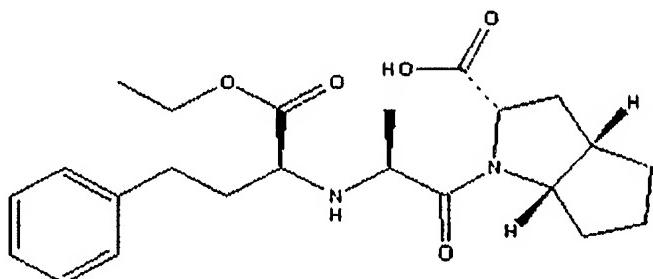
Properties of calcium sulphate are described in A. H. Kibbe, Handbook of pharmaceutical excipients, 73 – 76, American Pharmaceutical Association, Washington, and Pharmaceutical Press, London, 2000.

20

Calcium sulphate dihydrate is known as an inert diluent in compressed tablets. However, it was surprising that the stability of the tablets proved to be very satisfying.

DETAILED DESCRIPTION

25 The invention provides a pharmaceutical formulation comprising ramipril,



Compactrol as filling agent, and sodium hydrogen carbonate as stabilation agent.

The pharmaceutical formulation of the present invention comprises typically:

- 5 a) 0.1 – 5.0% w/w of ramipril;
 b) 50 - 95% w/w of Compactrol;
 c) 0.1 – 5.0% w/w of sodium hydrogen carbonate;
and optionally disintegrant (e.g. starch), binder and/or lubricant (e.g. sodium stearyl fumarate).

10

The formulation optionally also includes a diuretic, such as hydrochlorothiazide or piretanide.

For the tablet formulation containing 1.25 mg ramipril, the preferred amount of ramipril is 0.5-1.5% w/w, the amount of Compactrol is 85-90% w/w, the amount of sodium hydrogen carbonate is 0.5-1.5% w/w, the amount of starch pregelatinised is 7-13% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

- 20 For the tablet formulation containing 2.5 mg, 5 mg and 10 mg ramipril, the preferred amount of ramipril is 1.4-2.5% w/w, the amount of Compactrol is 78-95% w/w, the amount of sodium hydrogen carbonate is 1.4-2.5% w/w, the amount of starch pregelatinised is 7-13% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

25

- For the tablet formulation containing 2.5 mg ramipril/2.5 mg hydrochlorothiazide and 5 mg ramipril/25 mg hydrochlorothiazide, preferred amount of ramipril is 1.4-2.5% w/w, the amount of hydrochlorothiazide is 8.5-10.5% w/w, the amount of Compactrol is 65-75% w/w, the amount of sodium hydrogen carbonate is 1.0-2.5% w/w, the amount of starch pregelatinised is 12-18% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

For the tablet formulation containing 5 mg ramipril and 6 mg piretanide, the preferred amount of ramipril is 1.5 – 2.5% w/w, the amount of piretanide is 1.8

– 3.0% w/w, the amount of Compactrol is 65-85% w/w, the amount of sodium hydrogen carbonate is 3.0-5.0% w/w, the amount of starch pregelatinised is 10-20% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

- 5 Since ramipril is susceptible to certain types of degradation, there are several impurities formed during the manufacturing process and storing of the tablet. It is of high importance to minimize this degradation. The strength of different excipients was adjusted until a useful formulation was found.
- 10 There are certain criterias that these compounds are not allowed to exceed. The present formulation has proved to be stable.

Ramipril diketopiperazine is one of the compounds formed via degradation. The present formulation proved to be especially stable with regard to 15 formation of the diketopiperazine.

EXAMPLES

The following example is merely illustrative of the present invention and it 20 should not be considered as limiting the scope of the invention.

Example 1

Formulation for 1.25 mg ramipril tablets

25	Ramipril	0.96%
	Compactrol	87.08 % w/w
	Sodium hydrogen carbonate	0.96% w/w
	Starch pregelatinised	10.00% w/w
30	Sodium stearyl fumarate	1.00% w/w

Example 2

Formulation for 2.5 mg, 5 mg and 10 mg ramipril tablets

5	Ramipril	1.9% w/w
	Compactrol	85.2 % w/w
	Sodium hydrogen carbonate	1.9% w/w
	Starch pregelatinised	10.0% w/w
	Sodium stearyl fumarate	1.0% w/w

10

Example 3

Formulation for 2.5/12.5 mg and 5/25 mg ramipril hydrochlorothiazide (HCT) tablets

15	Ramipril	1.9% w/w
	Hydrochlorothiazide	9.6% w/w
	Compactrol	70.5 % w/w
	Sodium hydrogen carbonate	1.9% w/w
20	Starch pregelatinised	15.0% w/w
	Sodium stearyl fumarate	1.0% w/w

Example 4

25 Formulation for 5/6 mg ramipril piretanide tablets

30	Ramipril	1.9% w/w
	Piretanide	2.3% w/w
	Compactrol	76 % w/w
	Sodium hydrogen carbonate	3.7% w/w
	Starch pregelatinised	15% w/w
	Sodium stearyl fumarate	1% w/w

Example 5

Stability of 5 mg and 10 mg tablets prepared in Example 2 and of marketed preparation were tested at 40°C and 75% relative humidity (RH) for six months. Conversion of ramipril into ramipril diketopiperazine was assayed and measured as relative amount of initial amount of ramipril.

5 mg

	Assay	Ramipril diketopiperazine
10 Tablets from Ex. 2	4.0%	0.478-1.06%
Marketed prepn**.	4.0%	2.77%

10 mg

	Assay	Ramipril diketopiperazine
15 Tablets from Ex. 2	4.0%	0.471-0.806%
Marketed prepn**.	4.0%	2.27%

**Ramtib™ ramipril 5 and 10 mg tablets

20

The example demonstrates a very good stability with regard to ramipril diketopiperazine formation.

CLAIMS

1. A tablet formulation comprising:

- a) 0.5 – 5.0% w/w of ramipril;
- b) 50 - 95% w/w of calcium sulphate dihydrate; and
- c) 0.1 – 5.0% w/w of sodium hydrogen carbonate,

5 optionally in combination with a disintegrant, binder and lubricant and other excipients.

10 2. The tablet formulation of claim 1, wherein the calcium sulphate dihydrate is Compactrol.

3. The tablet formulation of claim 1 or claim 2, additionally in combination with a diuretic.

15 4. The tablet formulation of claim 3, wherein the diuretic is hydrochlorothiazide.

5. The tablet formulation of claim 3, wherein the diuretic is piretanide.

20 6. The tablet formulation of any of claims 1 to 5, wherein the disintegrant and binder is pregelatinised starch.

25 7. The tablet formulation of any of claims 1 to 6, wherein the lubricant is sodium stearyl fumarate.

8. The tablet formulation of claim 1 or claim 2 containing 1.25 mg ramipril, wherein the amount of ramipril is 0.5-1.5% w/w, the amount of Compactrol is 85-90% w/w, the amount of sodium hydrogen carbonate is 0.5-1.5% w/w, the 30 amount of starch pregelatinised is 7-13% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

9. The tablet formulation of claim 1 or claim 2 containing 2.5 mg, 5 mg or 10 mg ramipril, wherein the amount of ramipril is 1.4-2.5% w/w, the amount of

Compactrol is 78-95% w/w, the amount of sodium hydrogen carbonate is 1.4-2.5% w/w, the amount of starch pregelatinised is 7-13% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

5 10. The tablet formulation of any of claims 1 to 4, containing 2.5 mg ramipril/2.5 mg hydrochlorothiazide or 5 mg ramipril/25 mg hydrochlorothiazide, wherein the amount of ramipril is 1.4-2.5% w/w, the amount of hydrochlorothiazide is 8.5-10.5% w/w, the amount of Compactrol is 65-75% w/w, the amount of sodium hydrogen carbonate is 1.0-2.5% w/w, the
10 amount of starch pregelatinised is 12-18% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

11. The tablet formulation of any of claims 1 to 3 and 5, containing 5 mg ramipril and 6 mg piretanide, the preferred amount of ramipril is 1.5 – 2.5% w/w, the amount of piretanide is 1.8 – 3.0% w/w, the amount of Compactrol is 65-85% w/w, the amount of sodium hydrogen carbonate is 3.0-5.0% w/w, the amount of starch pregelatinised is 10-20% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.
15

20

25